REMARKS

Claims 1, 2, 4-7, 12, 14-16, 18-21, 24, 27, 30, 32, 33, 35, 37, 39, 41, 45, 47-49, 51 and 53-59 are pending in the above-identified application, of which Claims 1, 2, 4-7, 12, 14-16, 18-21, 24, 27, 30, 32, 33, 35, 37, 39, 41 and 47-49 are withdrawn from consideration. Claims 45 and 54-59 stand rejected under 35 U.S.C. §112, first paragraph as discussed below. Claims 45 and 54-57 are amended to correct formatting errors in the recitation of the peptide sequences. New claims 66 and 67, which depend from Claim 45, are added. No new matter is added by way of this amendment. Upon entry of the response, Claims 1, 2, 4-7, 12, 14-16, 18-21, 24, 27, 30, 32, 33, 35, 37, 39, 41, 45, 47-49, 51, 53-59, 66 and 67 will be pending, Claims 1, 2, 4-7, 12, 14-16, 18-21, 24, 27, 30, 32, 33, 35, 37, 39, 41 and 47-49 remain withdrawn, and Claims 45, 54-59, 66 and 67 are presented for further examination.

Presentation of New Claims 66 and 67

New Claims 66 and 67, which depend from Claim 45, are added. Claim 66 recites, in relevant part, the method of Claim 45, wherein said administering comprises administering to said individual at least one peptide capable of binding an HLA molecule expressed in the individual. Support for the claim can be found throughout the specification and claims as originally filed, particularly, for example, at page 50, lines 27-35 of the specification. Claim 67 recites, in relevant part, the method of Claim 45, wherein the individual has at least one of tissue type HLA-A2 and HLA-A3. Support for the claim can be found throughout the specification and claims as originally filed, particularly, for example, at page 32, lines 25-28 of the specification. Accordingly, no new matter is added by way of these amendments.

In view of the foregoing, Applicants respectfully request consideration of the added claims.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph, Enablement

The rejection of Claims 45 and 54-59 is maintained under 35 U.S.C. §112, first paragraph, for allegedly lacking an enabling disclosure. Specifically, the Examiner asserts that although the ELISPOT assay is deemed to be a reliable method of determining if a T cell response has been generated, it alone is insufficient to show that the administration of a peptide would have the same effect and result "given the unsuccessful attempts by others in the field."

Applicants respectfully disagree and submit that the instant application teaches those skilled in the art how to make and use the full scope of the invention without undue experimentation.

Standard for Enablement

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention 'without undue experimentation'... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. M.P.E.P. §2164.08 (citing *In re Buchner*, 929 F.2d 1557 (Fed. Cir. 1993)). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be duly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

The Claims

The claims relate to methods of raising **a specific T-cell response against an epitope of ML-IAP** in an individual by administering a polypeptide that includes a specific peptide sequence selected from RLQEERTCK, RLQEERTCKV, QLCPICRAPV or VLEPPGARDV. A distinction exists between the claimed methods and the rejections of record that are based on interpreting the claims as reading on *in vivo* treatment. The claims specify polypeptides that are capable of raising a specific T-cell response against the recited epitope, but do not require that all specific T-cell responses will result in tumor cell destruction by CTL's in all cases. Thus, a specific T-cell response as claimed is distinct from a claim that requires a predictive, curative T-cell response in all cases. Accordingly, Claim 45 recites a method for raising a specific T-cell response against an epitope of ML-IAP (SEQ ID NO:1) in an individual, said method comprising the steps of administering to the individual a polypeptide capable of raising a specific T-cell response, said polypeptide comprising a peptide selected from the group consisting of: RLQEERTCK (SEQ ID NO:245), RLQEERTCKV (SEQ ID N0:297), QLCPICRAPV (SEQ ID NO:298), and VLEPPGARDV (SEQ ID NO:301); wherein said polypeptide comprises at the most 15 amino acids, and raising a specific T-cell response against an epitope of ML-IAP in the individual. Claims 54-59, 66 and 67 depend from Claim 45 and thus contain all the features thereof as well as additional features recited in the claims.

The ELISPOT assay is indicative of in vivo results

The Examiner alleges that although the ELISPOT assay is deemed to be a reliable method of determining if a T cell response has been generated, it "alone is insufficient to show that the administration of a peptide would have the same effect and result given the unsuccessful attempts by others in the field." Applicants respectfully disagree.

Applicants submitted an Information Disclosure Statement (IDS) with the response filed October 22, 2007, containing three references that demonstrate the ability of HLA-restricted peptides to induce a T-cell response in patients. Anderson *et al* (2000. *Cancer Research* 6: 869-872, hereinafter referred to as "Anderson *et al*"), Wobser *et al* (2006. *Cancer Immunology Immunotherapy* 55:1294-1298, hereinafter referred to as "Wobser *et al*") and Otto *et al* (2005. *Vaccine* 23: 884-889, hereinafter referred to as "Otto *et al*") each describe detection of specific T-cell reactivity in patients suffering from leukemia, pancreatic cancer, and melanoma, respectively, against antigens derived from survivin, an apoptosis inhibitor overexpressed in most human cancers. In the references, the ELISPOT assay is conducted to measure both spontaneous T-cell responses and T-cell responses induced by vaccination using a peptide. The difference between spontaneous T cell responses compared to induced T cell responses lies in the origin of the sample analyzed, which can be obtained from a cancer patient not subjected to any vaccination therapy, or prior to such therapy and after such therapy.

Anderson *et al* discloses the analysis of several survivin epitopes, or analogues thereof. Those peptides which demonstrated HLA-A2 binding, or analogues thereof, were examined for the ability to generate CTL reactivity in chronic lymphatic leukemia (CLL) and melanoma (Mel) patients by ELISPOT assay. Figures 1, 2, 3 and 4 show the results of ELISPOT assays detecting the presence of a spontaneous T-cell response in patients CLL1, CLL2, CLL3, Mel1, Mel2 and Mel3 towards the peptides Sur1, Sur1L2, Sur1M2 and/or Sur9. Each individual displays T cell activity towards one or more of the peptides. As seen from below, such spontaneous T-cell activity is indicative for the ability of a peptide to induce an *in vivo* T-cell response in a (different) cancer patient.

Otto *et al* and Wobser *et al* both disclose the ability of the peptide named Sur1M2 to induce an *in vivo* T-cell response by vaccination. For example, as seen from Figure 2 of Otto *et al* and Figure 2B of Wobser *et al*, vaccinations using Sur1M2 lead to a drastic increase in reactive T-cells as measured by ELISPOT assays.

The references illustrate the connection between detecting spontaneous *in vivo* T-cell responses to specific peptides and administration of those peptides to patients, resulting in induction of specific T-cell responses *in vivo*. Anderson *et al.* teaches spontaneous *in vivo* T-cell response to specific survivin epitopes, while Otto *et al.* and Wobser *et al.* teach induction of an *in vivo* T-cell response by vaccination with specific survivin peptides included in the study of Anderson *et al.* Accordingly, the art clearly demonstrates that ELISPOT assay results are correlated to and predictive of induction of a peptide-specific *in vivo* T-cell response.

As acknowledged in a previous Office Action, the specification supplies numerous examples of ELISPOT data relating to the claimed methods. "The specification discloses detection of a CTL response against the peptides of SEQ ID Nos 245, 297, 298, and 301 in peripheral blood cells from melanoma patients (examples 2 and 3)." (*See* Office Action issued July 20, 2007, page 6). For example, Figure 1 depicts T-cell response against the ML-IAP_{280} (QLCPICRAPV) peptide as measured in an ELISPOT assay in peripheral blood lymphocytes (PBLs) from the melanoma patient FM3 (FIG. 1A) or FM72 (FIG. 1B) and in tumor-infiltrating lymphocytes (TILs) from the melanoma patient PM9 (FIG. 1C) or FM72 (FIG. 1D). Similarly, Figure 2 shows T-cell response as measured in ELISPOT against the peptides ML-IAP_{280} (QLCPICRAPV), ML-IAP_{245} (RLQEERTCKV), ML-IAP_{230} (VLEPPGARDV) and ML-IAP_{90} (RLASRYDWPL) in TIL samples from nine patients and in PBL samples from two patients. Figure 3 shows T-cell response against the MP-$IAP_{245-253}$ (RLQEERTCK) peptide as measured in an ELISPOT assay using PBLs from 14 melanoma patients. Furthermore, Figure 4 depicts *in situ* detection of ML-IAP-reactive CTL in primary tumors from two HLA-A2-positive melanoma patients, and Figure 5 illustrates cytolytic capacity of ML-IAP-specific CTL. The detected T-cell activities represent the spontaneous T-cell activity towards these peptides present *in vivo* in the cancer patients from which cell samples have been derived.

Furthermore, the specific peptides recited in the claims are not randomly selected but are supported by a theoretic reasoning that is accepted by those of skill in the art, specifically, *in vitro* binding activity towards an HLA allele and the detection of specific T-cell responses towards these peptides. A match between HLA type in a subject and specificity of administered peptide or peptides to the subject are two parameters that contribute to the likelihood of producing an efficient and specific *in vivo* T-cell response. Claims 66 and 67 are added to

include these parameters in raising a specific T-cell response against an epitope of ML-IAP, as claimed.

Applicants respectfully submit that, taken together, the references and the data of the instant specification, including the disclosure provided in Examples 2 through 5, are sufficient to teach those skilled in the art to make and use the full scope of the claimed invention, without undue experimentation.

The art does not illustrate that generation of an in vivo CTL response is unpredictable

The Examiner asserts the insufficiency of an ELISPOT assay to alone show that administration of a peptide would generate a T cell response "given the unsuccessful attempts by others in the field" by alleging that "the prior art of record teaches that several attempts by others have failed to generate appropriate CTL responses *in vivo* against specific epitopes, whereby only a limited number of epitopes were successful in generating an [*sic*] response." Applicants respectfully disagree with the Examiner's assertion.

Applicants assume that the "prior art of record" noted by the Examiner refers to the art cited in the Office Action mailed on July 20, 2007. Applicants had previously rebutted the relevance and suitability of these references for establishing unpredictability in the art for inducing a T-cell response using cancer-associated epitopes and peptides in the response filed October 22, 2007. For the convenience of the Examiner, the argument is reproduced below:

> In Apostolopoulos et al [1998. *Nat Med* 4(3):315-320] and Jager et al [2000. *PNAS* 97:12198-12203], . . . a clear correlation between the presence or absence of antibodies towards the target peptide and the induction of a specific T-cell response is demonstrated. The outcome of administration of a tumor peptide antigen is thus not unpredictable as the Examiner concludes. Bodey et al [2000. *Anticancer Research* 20:2665-2676] . . . actually states that general immune activation directed against the target antigen has been demonstrated in most cases. It is further noted that such vaccines may be used in combination with other therapies. Claim 45 is directed towards a specific T-cell response against an epitope of ML-IAP in an individual, not towards complete regression of tumors by cell lysis of all tumor cells. Semino et al [1993. *Journal of Biological regulators and Homeostatic Agents* 7:99-105] . . . relates to treatment of patients with interferons, and thus does not relate to the induction of a specific T-cell response. Both Ohlen et al [2001. *J Immunol* 166:2863-2870] and Antonia et al [1995. *International Immunology* 7:715-725], cited by the Examiner as allegedly demonstrating the ineffectiveness of CTLs in lysing tumor cells, discuss mechanisms involved in the development of tolerance to self proteins, not to cancer specific antigens such as ML-IAP. The expression of ML-IAP is cancer-specific,

> avoiding the problem of induction of tolerance to self proteins that is described in these references. This is the reason [why] ML-IAP is a particularly good target. The outcome of administration of a tumor antigen peptide as ML-IAP is thus not unpredictable as the Examiner alleges. Moreover, tumor cell lysis *in vivo*, which was not observed in the references cited by the Examiner, is not claimed in the present application, as stated above.

Thus, in view of the foregoing, the cited references do not demonstrate with sufficient clarity the alleged unpredictability in the art.

Applicants have discussed Otto *et al.* and Wobser *et al.* above, which teach induction of a T-cell response *in vivo* by vaccination with a specific survivin peptides. In addition, Applicants herewith submit two additional references in support of using peptides to induce a T cell response. Keilholz *et al* (2006. *Clin Cancer Res* 12(7 Suppl):2346s-2352s) discusses spontaneous tumor directed T-cell responses and the knowledge derived therefrom, supporting the use of cancer antigens to which a spontaneous T-cell response has been detected. Slingluff *et al* (2006. *Clin Cancer Res* 12(7 Suppl):2342s-2345s) discuss the results obtained with peptide vaccines in melanoma immune therapy. Although clinical responses have only been observed in few cases, the trials has shown that $CD8^+$ T-cell response can be generated by vaccination with peptide or dendritic cell vaccines.

Taken together, these references indicate that specific T-cell responses can in fact be generated against peptide antigens. Accordingly, Applicants respectfully submit that the specific peptide antigens can be predicted to be capable of inducing specific T-cell responses and that detection of a spontaneous T-cell response to a given peptide is indicative of the ability of said peptide to induce a T-cell response *in vivo*.

In view of the foregoing, it is respectfully submitted that Applicants have adequately enabled the claimed invention. Withdrawal of the rejection is thus requested.

CONCLUSION

Applicant submits that the present Application is in condition for allowance and respectfully request the same. If any issues remain, the Examiner is cordially invited to contact Applicant's representative at the number provided below in order to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 04-0258.

Respectfully submitted,

Dated: February 3, 2009

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